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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 08/405,454
Filing Date: March 15, 1995
Appellant(s): SULLIVAN ET AL.

Michael Siekman
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/6/2004.

1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. However, appellant has failed to disclose that in the previous Appeal that the rejection of previously pending claims 45-47 under 35 U.S.C. section 103 over Sullivan in view of Coulter was affirmed.

(3) Status of Claims

The statement of the status of the claims contained in the brief is partially correct. The brief fails to disclose that claims 1-39,43-49 and 51-53 have been cancelled.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is partially correct. Regarding appellants comments in page 3, second paragraph of the Brief, the prior art recognized that Fab could be used to neutralize a large molecular weight toxin in vivo (Coulter et al. disclosed that a composition of F(ab) fragments of antibody against textilotoxin (a large molecular weight snake toxin) could be used in vivo to neutralize said toxin(see pages 201-203)). Regarding appellants comments about the specification, page 10, lines 14-21 (actually page 11), said quote refers to a comparison to a commercially purified antivenin, not whole antibody preparations per se. Table 3 of the specification actually demonstrates that depending on the dosage of toxin administered that F(ab) fragments do not necessarily provide a higher degree of protection than IgG (purified from the commercial antivenin) wherein said IgG is a "whole antibody".

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims cited in each of the two pending rejections stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Sullivan et al., Proc. West. Pharmacol. Soc., vol. 25, (1982), pp. 185-192.

Smith et al., Clin. Exp. Immunol., vol. 36, (1979), pp. 384-396.

Coulter et al., J. Immunol. Methods, vol. 59, (1983), pp. 199-203.

Stedman's Medical Dictionary, 23rd Edition, Williams and Wilkins Co., (1976), pp. 94.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims.

Rejections Under 35 U.S.C. § 103

A) Claims 40-42,50 are rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al. for the reasons elaborated in pages 9-10 of the BPAI decision mailed 1/29/2003.

B) Claims 40-42,50 are rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al. as evidenced by Stedman's Medical Dictionary (1977).

This rejection addresses the claims as actually encompassing an antivenom which is actually used to treat snakebite (a.k.a. neutralize the lethality of the venom of a snake of the Crotalus genus).

Sullivan et al. teach purified antivenin polyvalent antibodies derived from horse hyperimmune antisera against venom of the Crotalus genus (see Methods section, pages 185-187). These antibodies are predominantly IgG(T), because that is the predominant isotype found in hyperimmune horse antisera. A routineer would have immunized horses to produce said hyperimmune antisera because this is the art recognized procedure for producing antivenin. Sullivan et al. do not teach a F(ab) containing antivenin. The amendment filed 5/4/98, pages 3 and 4 establishes that the art recognized that the terms "antivenin" and "antivenom" refer to the same product.

Coulter et al. teaches a method for producing F(ab) fragments that are free of Fc (see abstract). Coulter et al. teaches a composition of F(ab) fragments of antibody against textilotoxin (a snake toxin) (see pages 201-203). Stedman's Medical Dictionary defines antivenin as "an antitoxin specific for an animal or insect toxin"(page 94). Therefore the composition taught by Coulter et al. is an antivenin. The F(ab) composition (page 201, third paragraph) was derived from polyclonal antisera against textilotoxin (page 199, second paragraph). The F(ab) produced by said method were free of Fc and extraneous protein (see Abstract). A routineer would have assayed for Fc by immunoelectrophoresis using anti-Fc antibodies or any other art recognized procedure.

Smith et al. teaches the advantages of F(ab) fragments for the neutralization and clearance of toxic substances in therapeutic applications (see page 393, first paragraph, Discussion section). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced antivenom compositions consisting of F(ab) fragments because Sullivan et al. teach purified antivenin polyvalent antibodies derived from horse hyperimmune antisera against venom of the Crotalus genus, Coulter et al. teaches a method for producing antivenin F(ab) fragments that are free of Fc, and Smith et al. teaches the advantages of F(ab) fragments for the neutralization and clearance of toxic substances in therapeutic applications. One of ordinary skill in the art would have been motivated to do the aforementioned because Smith et al. teaches that,

"Relatively rapid clearance of Fab fragments can be used to advantage when the objective is rapid neutralization and clearance of a toxic substance, and purified sheep digoxin specific Fab fragments have been utilized clinically for the reversal of advanced digoxin intoxication. This therapeutic approach is based on similar binding properties and the postulated lesser immunogenicity of Fab compared with IgG. For urgent clinical situations such as life threatening digitalis-toxic cardiac arrhythmias, the present study indicates that Fab has another important advantage-more rapid and extensive distribution to its presumed site of action in the interstitial space." (page 393). Further motivation is provided by the teaching of Coulter et al. that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). In addition, Sullivan et al. teach that reducing the immunogenicity of polyvalent horse antivenin is an important goal, due to immune reactions that limit the clinical efficacy of antivenin preparations which contain only partially purified hyperimmune horse antisera (see page 185, first paragraph).

(11) Response to Argument

Rejections Under 35 U.S.C. § 103

B) Claims 40-42,50 are rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al. as evidenced by Stedman's

Medical Dictionary (1977). Appellants arguments have been considered and deemed not persuasive.

This rejection addresses the claims as actually encompassing an antivenom which is actually used to treat snakebite (a.k.a. neutralize the lethality of the venom of a snake of the Crotalus genus). As per the decision of the BPAI mailed 1/29/2003, the prior art renders obvious the particular Fab recited in the claims (Fab fragments which bind specifically to a venom of the Crotalus genus with the particular degree of purity recited in the claims).

Regarding appellants comments about CroFab (page 7 of the Brief) CroFab is a **ovine** Fab antivenom wherein ovine antivenom are **not disclosed in the specification of the instant invention**. Thus, **CroFab is a preparation that is not even disclosed in the specification**. Furthermore, the submitted materials indicate that an Orphan projects grant award was given to conduct clinical trails related to CroFab. Thus, it was not clear at the time (almost 10 years after the effective filing date of the instant application) whether CroFab had any particular degree of efficacy because clinical trials had not been conducted. In addition, none of the filed Orphan drug papers related to CroFab state that it has any properties better than any art known antivenom. The Orphan drug program addresses drugs that would not be developed by large companies because the target patient population is sufficiently small that large drug companies would not

necessarily be interested because of financial considerations. That is the purpose of the orphan drug program.

Regarding the issue of serum sickness, Smith et al. disclose that "Furthermore, Fab fragments are significantly less immunogenic than the parent IgG population" (see page 384). Smith et al. disclose that "It is reassuring in this regard that none of the baboons or rabbits tested showed any signs of anaphylactic reaction ...". Thus, the prior art **already recognized that Fab were less immunogenic than Ig from which the Fab were derived and less likely to cause serum sickness**.

Regarding appellants comments in pages 7-9 of the instant Brief, the following comments are made. Regarding F(ab)2 containing antivenom, the claimed invention is not drawn to F(ab)2 it is drawn to Fab. However, regarding the Smith declaration and F(ab)2 based antivenom, there is no teaching in said declaration that F(ab)2 based antivenom are less effective than whole immunoglobulin based antivenom. In fact, the Smith declaration indicates that such preparations have been sold (and presumably used) since 1969 (see section 7). Regarding comments about F(ab)2 in the First Russell declaration and Sullivan declarations, said statements are directly contradicted by their own statements in the instant application (Sullivan and Russell are the inventors of the instant application). For example, the specification, page 8, lines 5-8 state:

"Such F(ab)2 fragments should also afford greater protection against venom-induced pathophysiology than the commercial antivenin."

Also see original claim 28 which is drawn to a F(ab)2 antivenin against Crotalus. Thus appellants arguments regarding the issue of F(ab)2 antivenom versus intact antibody antivenom are contradicted by the teachings of their own specification.

Regarding appellants comments about "venom depot effect" and use of Fab to neutralize toxins, Smith et al. disclose that because of smaller size, administered Fab are actually more rapidly and extensively distributed throughout the body than IgG (see page 395). Thus, Fab would actually be more likely to reach toxins distributed in various nonvascular compartments of the body. Regarding the kinetics of elimination of Ig versus Fab, Smith et al. teach that rapid clearance of Fab "can be used to advantage when the object is rapid neutralization and clearance of a toxic substance" (see page 393). Regarding the issue of bivalency of F(ab)2, there is no evidence of record that cross linking of antibody fragments is required for toxin neutralization. Certainly, both Smith et al. and Coulter et al. which demonstrate toxin neutralization using Fab, would contradict the need for cross linking of antibody binding fragments for toxin neutralization. The Smith et al. and Coulter et al. publications clearly disclose use of Fab in vivo to neutralize a small or large sized toxin molecule.

Regarding appellants comments in pages 10-14 of the Brief, said comments are based on an erroneous interpretation of the Faulstich et al. and Balthazar et al. publications. The comments in the Sullivan and Russell declarations are clearly based on an erroneous interpretation of the Faulstich et al. and Balthazar et al. publications.

Regarding the Faulstich et al. reference said reference teaches that **monoclonal antibody against alpha amatoxin cannot be used to treat alpha amatoxin and that F(ab) obtained from said antibody also cannot be used to treat alpha amatoxin.** Thus, the circumstances surrounding treatment of alpha amatoxin poisoning differ from treatment of snake venom because Sullivan et al. teach that the use of antibody to treat snake venom is well known in the art and Coulter et al. teach that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). Regarding comments about Balthazar et al., **Balthazar et al. refer to alpha amatoxin, which is a toxin which cannot be treated with antibodies as shown by Faulstich et al.** The circumstances surrounding treatment of alpha amatoxin poisoning differ from treatment of snake venom because the use of antibody to treat snake venom is well known in the art and Coulter et al. teach that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). Furthermore, Balthazar et al. teach that the use of drug-binding antibodies and antibody fragments for the treatment of drug intoxication is well known. (see Abstract, last sentence). In addition, Coulter et al. teach that F(ab) which neutralizes a large molecular weight protein snake toxin can be made and that said antivenom can work in vivo to neutralize snake toxin (see page 202, third paragraph). The various comments in the First Russell declaration and Sullivan declaration about why F(ab) would not work as disclosed in the instant Brief are **based on the aforementioned misinterpretation/distortion of the data provided in the Balthazar**

et al. and Faulstich et al. references. In the absence of support from the Balthazar et al. and Faulstich et al. references, the hypotheses about why Fab would not work are unsubstantiated allegations. There is no evidence of record that Fab derived from an Ig antivenom which neutralized toxin would have any negative effect when said Fab were administered in vivo. Regarding appellants comments that the experiments disclosed by Coulter et al. used toxin and antibody or Fab that were first mixed before in vivo injection, **the art already recognized that the antivenom from which the Fab would have been derived could bind Crotalus venom, and Smith et al. reference indicates that Fab actually have a more favorable distribution in vivo than intact antibody with regards to the neutralization of toxin.** Furthermore, if a deleterious systemic redistribution of Fab/venom complexes in vivo was to occur, it would have occurred in the experiments disclosed by Coulter et al., because the complexes were present in vivo. Regarding comments about Sorkine et al., **Sorkine et al. disclose that Fab was successfully used to neutralize toxin in vivo, irregardless of whether the assay used premixing of Fab and toxin or separate in vivo administration of Fab and toxin. Sorkine et al. disclose that "One explanation is the different kinetics of these fragments. The smaller size of Fab results in faster diffusion and a greater volume of distribution".**

Thus, Sorkine et al. confirm the teachings of Smith et al. that Fab actually have a more favorable distribution in vivo than intact antibody with regards to the neutralization of toxin. In addition, the art already recognized that the antivenom from which the Fab

would have been derived could bind Crotalus venom, and Smith et al. reference indicates that Fab actually have a more favorable distribution in vivo than intact antibody with regards to the neutralization of toxin. Furthermore, Sorkine et al. actually confirm that with regards to Fab that the in vitro mixture of the antibody and toxin prior to administration mirrors the effect seen when Fab and toxin are administered separately in vivo. Regarding appellants comments, antisera against Crotalus toxin which contained antibodies to neutralize said toxin/toxins was already known in the art. Smith et al. teach that F(ab) are less immunogenic than the antibody from which they are derived (see page 395). Smith et al. teaches that,

"Relatively rapid clearance of Fab fragments can be used to advantage when the objective is rapid neutralization and clearance of a toxic substance, and purified sheep digoxin specific Fab fragments have been utilized clinically for the reversal of advanced digoxin intoxication. This therapeutic approach is based on similar binding properties and the postulated lesser immunogenicity of Fab compared with IgG." (page 393).

Thus, appellants arguments are based on misinterpretations of the Faulstich et al. and Balthazar et al. references and declarations from Russell and Sullivan which provide various unsupported hypotheses about why Fab antivenom would not work, without providing any evidence to support said conjecture. In addition, the Russell and Sullivan declarations actually contradict some of the very statements made in the specification (eg. see comments regarding F(ab)2).

Regarding appellants comments in pages 4-6, 13-16 of the instant Brief, Sullivan et al. teach purified antivenom polyvalent antibodies derived from horse hyperimmune antisera against venom of the Crotalus genus (see Methods section, pages 185-187). Sullivan et al. disclose that said preparation can be used as antivenom to treat Crotalidae envenomation (see page 185, first paragraph). Thus, while Crotalidae venom contains a complex mixture of toxins, the antivenom taught by Sullivan et al. contains **all the necessary antibodies to neutralize the toxicity/lethality of said mixture**. Coulter et al. teach that F(ab) which neutralizes a large molecular weight protein snake toxin can be made and that said antivenom can work in vivo to neutralize the lethality of snake toxin (see page 202, third paragraph). Smith et al. teach that Fab fragments can be used to neutralize digoxin (low molecular weight potential toxin)(see Summary). Smith et al. also teaches that relatively rapid clearance of Fab fragments can be used to advantage when the objective is rapid neutralization and clearance of a toxic substance (see page 393, Discussion section) indicating that Smith et al. believed that Fab could be used for the neutralization of toxic substances other than digoxin. Furthermore, Smith et al. indicated that Fab and the intact antibody from which the Fab were derived would be expected to have similar binding properties (see page 393, Discussion section). Thus, the art recognized that when an intact antibody has been shown to have the capability of neutralizing a toxin, that the Fab derived from said antibody will also be able to neutralize said toxin. Furthermore, based on the teachings of Coulter et al. and

Smith et al. it appears that use of Fab to neutralize toxin (wherein the intact antibody had already been shown to be capable of neutralizing said toxin) would be equally applicable to large and small toxin molecules. There is no actual evidence of record that establishes that it would be unpredictable whether Fab derived from a known antivenom would have antivenom activity seen in the preparation from which it was derived.

Regarding motivation to create the claimed invention, one of ordinary skill in the art would have been motivated to create the claimed intention because Smith et al. teaches that,

"Relatively rapid clearance of Fab fragments can be used to advantage when the objective is rapid neutralization and clearance of a toxic substance, and purified sheep digoxin specific Fab fragments have been utilized clinically for the reversal of advanced digoxin intoxication. This therapeutic approach is based on similar binding properties and the postulated lesser immunogenicity of Fab compared with IgG. For urgent clinical situations such as life threatening digitalis-toxic cardiac arrhythmias, the present study indicates that Fab has another important advantage-more rapid and extensive distribution to its presumed site of action in the interstitial space." (page 393). Further motivation is provided by the teaching of Coulter et al. that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). In addition, Sullivan et al. teach that reducing the immunogenicity of polyvalent horse antivenin is an important goal, due to immune reactions that limit the

clinical efficacy of antivenin preparations which contain only partially purified hyperimmune horse antisera (see page 185, first paragraph).

A) Claims 40-42,50 are rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al.

Regarding appellants comments, the composition rendered obvious by the instant rejection would "neutralize the lethality of the venom of a snake of the Crotalus genus" because it contains the same ingredient as that recited in the claims (Fab which binds Crotalus venom of the degree of purity recited in the claim). Regarding the preamble of claim 40, it is unclear as to why said preamble should be given any more weight than the old preamble, because both preambles merely refer to an intended use for the claimed invention. IgG(T) is horse derived immunoglobulin (see page 6 of the BPAI decision mailed 1/29/2003, page 6, footnote). Also, it is noted that Coulter et al. discloses that the Fab is produced in a quantity that can used to neutralize the lethality of a snake toxin in vivo (see page 201, *Mouse protection assays*).

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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April 27, 2005

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